

226
BAB

PATENT SPECIFICATION

1,199,871



NO DRAWINGS

1,199,871

Date of Application (No. 20551/68) and filing Complete Specification: 1 May, 1968.

Two Applications made in United States of America (Nos. 637,649 and 637,650) on 11 May, 1967.

Complete Specification Published: 22 July, 1970.

Index at acceptance:—C2 C(3C5A2, 3C5C8, 3C5E2)

International Classification:—C 07 c 149/32

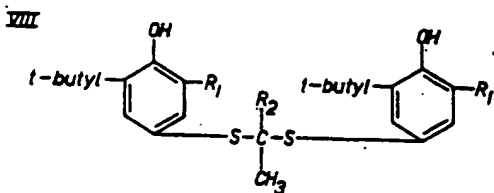
COMPLETE SPECIFICATION

Improvements in or relating to Sulfur-Containing Bisphenols

We, CONSOLIDATION COAL COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of Koppers Building, Pittsburgh, State of Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

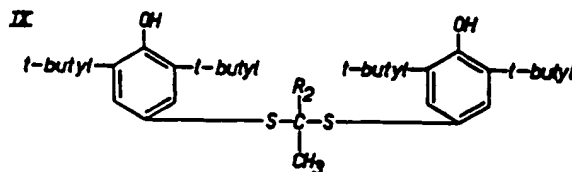
This invention relates to a new and useful group of sulfur-containing bisphenols. United States Patents Nos. 2,278,224 and 2,472,318 describe compounds defined by the formula $DR_xR'_xRD$, in which R is an aryl or alkyl aryl, or a substituted aryl or alkyl aryl group, x is a sulfur, oxygen or tellurium, but preferably a sulfur group, R' is an alkyl or substituted alkyl group and D is an inhibitor group taken from the class of hydroxy, amino, sulfide, disulfide or polysulfide groups. The utility set forth in the patents for the described compounds is stabilization of lubricating oils.

According to the present invention there is provided a compound having the general formula:



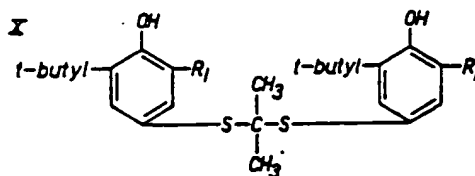
where R₁ is an alkyl group containing 1 to 4 carbon atoms, R₂ is hydrogen or an alkyl group containing 1 to 3 carbon atoms and the group t-butyl is a tertiary butyl group.

There is further provided a compound having the general formula:



where R₂ is hydrogen or an alkyl group containing 1 to 3 carbon atoms and t-butyl represents a tertiary butyl group.

In addition, the present invention provides a compound having the general formula:

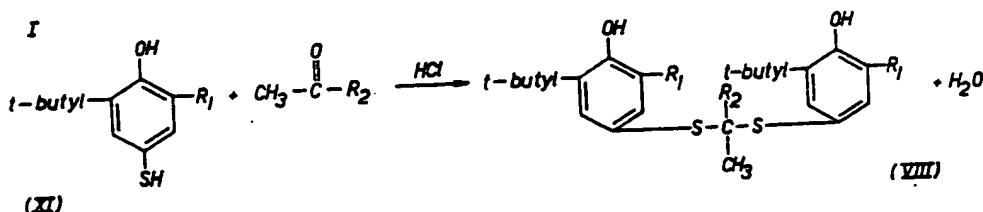


where R_1 is an alkyl group containing 1 to 4 carbon atoms and *t*-butyl is a tertiary butyl group.

The chemical compounds of the present invention possess the property of lowering the cholesterol content of blood, in marked contrast to the other members of the genus to which they belong.

The compounds of the present invention may be readily prepared as follows. The starting material is the appropriate mercaptophenol which may be prepared by any one of several known methods. For details, see *Organic Reactions*, Vol. III, Chapter 6, by Roger Adams et al; also the article by Müller et al, entitled "Untersuchungen an schwefelhaltigen Aroylen mittels der Elektronenresonanz" in *Liebigs Annalen* (1961, Bd. 645, p. 79); and U.S. Patent No. 3,129,262.

The mercaptophenol is then reacted with the appropriate carbonyl compound in the presence of an acid catalyst, preferably a strong acid catalyst. Most preferably, the strong acid catalyst is hydrochloric acid, but, alternatively the strong acid catalyst may be sulfuric acid, perchloric acid or a strong acid cationic exchange resin. For example, the mercaptophenol can be dissolved in a minimum of inert solvent to give a homogeneous reaction mixture. Concentrated hydrochloric acid (0.05 mole per mole of mercaptophenol) and at least a stoichiometric amount of the appropriate carbonyl compound are added, the former serving as a strong acid catalyst. The reaction is as follows:—

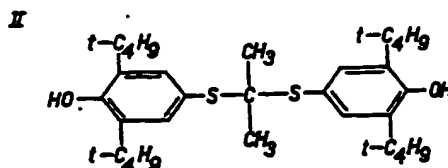


where R_1 is an alkyl group containing 1 to 4 carbon atoms and R_2 is hydrogen or an alkyl group containing 1 to 3 carbon atoms. The group "*t*-butyl" is a tertiary butyl group. In the above representation of the reaction the numerals (VIII) and (XI) refer to the specific molecules adjacent thereto while the numeral (I) refers to the reaction as a whole. Initially, the reaction is mildly exothermic, but external heating is thereafter required to maintain the reaction temperature. Reaction times of about one to six hours are usually required. The product is then recovered from the reaction mixture in conventional fashion.

The following examples illustrate the preparation of the novel compounds of this invention. In each example, the chemical name and structural formula of the compound are first given. The identity of the compound produced in each example was established by conventional methods of analysis.

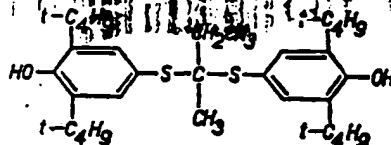
EXAMPLE 1

Preparation of:
2,2-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-propane



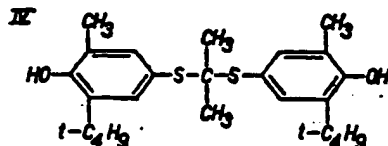
4-Mercapto-2,6-di-*t*-butylphenol (47.5 g., 0.2 mole) was dissolved in 50 ml. of methanol at 50°C.; and 1.0 ml. of concentrated HCl was added. Then, acetone (5.8 g., 0.1 mole) was added with a resultant temperature rise to 60°C. The reaction mixture was maintained at 60–65°C. for an hour and a half by heating; and was then allowed to cool. Ten ml. of 10% aqueous sodium bicarbonate was added. The mixture was diluted with water and extracted with ether. The residue from the evaporation of the ether solution, a yellow viscous oil, was recrystallized from ethanol to form a white crystalline solid. This first crop of crystalline product weighed 33.0 g. and had a melting point of 124.5°–126°C. The liquor from the crystallization was concentrated by evaporation to yield 12.0 g. of a second crop of fine, slightly colored crystalline product. The total yield was 87.4%. When recrystallized from isopropyl alcohol, the product had a melting point of 125°–126.5°C.

EXAMPLE 2
Preparation of:
2,2-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-butane



4-Mercapto-2,6-di-*t*-butylphenol (47.6 g.) was dissolved in 50 ml. of methanol. Ethyl methyl ketone (18.15 ml.) was added to the solution and then 8 ml. of 12N HCl was added causing a temperature rise from 16° to 26°C. The reaction mixture was heated to reflux (69°C.) and held there for two hours. It was then cooled below 50°C.; and 100 ml. of benzene was added. The mixture was transferred to a separatory funnel and washed three times with 100 ml. of water to remove the acid. The benzene phase was separated and dried over magnesium sulfate. Benzene was stripped off on a rotary evaporator. A clear yellow oil remained which weighed 53.3 g. The oil was dissolved in 100 ml. of ethanol. The ethanol solution was seeded, by the addition of previously formed crystals of the product, and cooled. Crystals formed which were collected by filtration and washed with 100 ml. of cold ethanol. They were then air dried for five hours, and dried in a vacuum desiccator for one hour, after which they weighed 29.2 g. and melted at 134.1°–135.8°C. The product was recrystallized from 150 ml. of hot ethanol. The crystals were washed with 100 ml. of ethanol. They were then air dried for 2-1/2 hours and in a vacuum desiccator for one hour. The final weight of the product was 22.5 g. (44.7% yield), and the final melting point was 135.0°–136.8°C.

EXAMPLE 3
Preparation of:
2,2-Bis-(3-*t*-butyl-5-methyl-4-hydroxyphenylmercapto)-propane



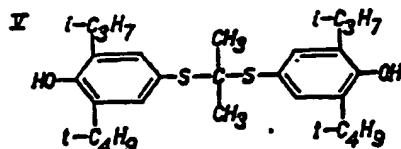
4-Mercapto-6-*t*-butyl-*o*-cresol (39.3 g., 0.2 mole) was dissolved in 30 ml. of methanol at room temperature, and 1 ml. of concentrated HCl was added. Then, acetone (5.8 g., 0.1 mole) was added with a resultant temperature increase from 27°C. to 46°C. The reaction mixture was maintained by heating at 42°–45°C. for 45 minutes, and then allowed to stand for several hours. Large colorless crystals were observed in the flask. The liquid portion of the mixture was decanted. The crystals were dissolved in ether, and the solution extracted with 10% NaOH, water washed to pH 7, dried, and filtered. The ether solution was evaporated to dryness. The residue, a slightly colored waxy solid, was extracted with 250 ml. of refluxing hexane. The hexane solution was allowed to cool to room temperature with resultant precipitation of 34.3 g. of a white powder which had a melting point of 156.5°–158.0°C.

The hexane filtrate was evaporated to about 30 ml., allowed to cool to room temperature. Slightly yellow crystals precipitated amounting to 3.0 g., and having a melting point of 153.5°—155.5°C. Based upon the two crops of crystals, the yield was 86%. A small sample of the product, recrystallized from isopropyl alcohol and dried in vacuo at 110°C., had a melting point of 155.5°—156.5°C.

EXAMPLE 4

Preparation of:

2,2-Bis-(3-isopropyl-5-*t*-butyl-4-hydroxyphenylmercapto)-propane

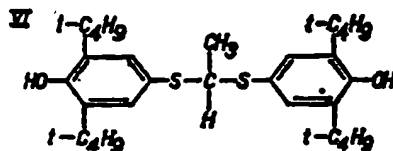


2-Isopropyl-4-mercapto-6-*t*-butylphenol (44.8 g.), 50 ml. of methanol, and 14.6 ml. of acetone were mixed. To the mixture, 8 ml. of 12N HCl was added causing a temperature rise from 26° to 41°C. The reaction mixture was heated for two hours to a final temperature of 54°C. The solution was cooled in a water bath. Benzene (100 ml.) was added to the solution in a separatory funnel, and the mixture washed three times with 100 ml of water to neutrality. The phases were separated, and the benzene phase was dried over magnesium sulfate. The magnesium sulfate was then filtered off, and the benzene was removed, first by stripping on a rotary evaporator and then by oil pump vacuum. A clear colorless, viscous oil remained which weighed 51 g. The oil was dissolved in 75 ml. of hot hexane and washed with 50 ml. of 10% caustic solution, followed by 100 ml. of water. The hexane solution was made slightly acidic with a few drops of HCl. It was then washed to neutrality with water and dried over magnesium sulfate. After the magnesium sulfate was filtered off, the hexane was stripped off under vacuum, leaving an oil which was dissolved in 60 ml. of hot methanol. The methanol solution was cooled. Deionized water was added in increments until crystals began to form. A total of 10 ml. of deionized water was necessary. The oil, containing a small amount of crystals, was cooled for completion of crystallization. The crystals were filtered and washed with 8 ml. of 85.7% methanol solution, and air dried. The weight of the crystals was 11.9 g., and they melted at 74°—77°C. The crystals were triturated with 60 ml. hexane and cooled. They were then filtered off and air dried. The dry product crystals weighed 9.1 grams and melted at 77.0°—79.8°C. A second crop of crystals was obtained from the methanol solution by adding cooled hexane to the solution and by further cooling. The slightly yellow crystals so obtained were filtered and air dried. They weighed 17.5 g. and melted at 74.2°—75.4°C. The two crops were dissolved in 25 ml. of hot hexane. The crystals which precipitated were recovered by filtration and air dried. The final weight of product was 25.2 grams (51.6% yield), and the melting point was 74.3°—78.6°C.

EXAMPLE 5

Preparation of:

1,1-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-ethane



4-Mercapto-2,6-di-*t*-butylphenol (47.5 g., 0.2 mole) was dissolved in 50 ml. of methanol at 50°C., and 1.0 ml. of concentrated HCl was added. Then, acetaldehyde (4.4 g., 0.1 mole) was added with no observable temperature rise from 53°C. The stirred solution was heated to maintain temperature at 50°—55°C. for two hours and then was allowed to cool to room temperature. Then, 9.5 ml. of 10% NaHCO₃ was added to neutralize the HCl. The mixture was diluted with 200 ml. of H₂O, extracted with ether, and the ether portion extracted with 10% NaOH to remove

unreacted mercaptophenol. The ether portion was water washed to pH 7, dried and evaporated to yield a yellow viscous oil (44.5 g.). This was redissolved in hot hexane, stirred with activated charcoal, filtered by gravity while hot, and again concentrated to a yellow solid (wt. 41 g., 82% yield).

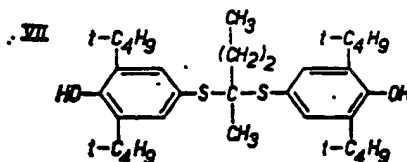
5

EXAMPLE 6

5

Preparation of:

2,2-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-pentane



10

To a stirred mixture of 47.6 g. of 4-mercapto-2,6-di-*t*-butylphenol, 50 ml. of methanol and 21.2 ml. of 2-pentanone was added 8 ml. of 12N HCl. A dense crystal slurry and a temperature rise from 20° to 26°C. resulted. After 1/2 hour of heating, an emulsion formed (at 53°C.) which, an hour later, became a very viscous oil. In another 5 minutes, a dense crystal slurry appeared. The total time was about 1.5 hours, and the final temperature was 54°C. The slurry was allowed to cool (with stirring) to room temperature. The crystals were filtered off, washed with 50 ml. of an 80% aqueous methanol solution and air dried. The crude crystals weighed 48.8 g. and melted at 129.2°—131.9°C. The product was dissolved in 200 ml. hot ethanol and hot filtered. The solution was cooled to room temperature and then placed in a refrigerator. The crystals were filtered off and washed with enough ethanol to cover the crystal cake. The final weight of dried crystals was 35.7 g. (65.7% yield). Their melting point was 133.0°—134.4°C.

10

15

15

20

20

25

25

The following table tabulates the per cent reduction of cholesterol in the blood of rodents effected by the use of compounds of this invention, and also the per cent reduction effected by the use of other compounds of the genus of which the compounds of the present invention are also members. The compound was added to commercial rodent chow at a level of 0.125% by weight, and the mice were allowed to feed ad libitum for two weeks. At the end of this period, serum cholesterol determinations were performed on all the mice.

Per Cent Cholesterol Reduction

30

30

Compound	% Reduction
EXAMPLE 1	
2,2-Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-propane	59
EXAMPLE 2	
2,2-Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-butane	42
EXAMPLE 3	
2,2-Bis-(3- <i>t</i> -butyl-5-methyl-4-hydroxyphenylmercapto)-propane	25
EXAMPLE 4	
2,2-Bis-(3-isopropyl-5- <i>t</i> -butyl-4-hydroxyphenylmercapto)-propane	22
EXAMPLE 5	
1,1-Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-ethane	19
EXAMPLE 6	
2,2-Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-pentane	12
2,2-Bis-(4-hydroxyphenylmercapto)-propane	0
2,2-Bis-[3,5-di-(<i>sec</i> -butyl)-4-hydroxyphenylmercapto]-propane	0
2,2-Bis-(3,5-dimethyl-4-hydroxyphenylmercapto)-propane	0
2,2-Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-heptane	0
α,α -Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-ethylbenzene	0
α,α -Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-toluene	0
2,2-Bis-(3,5-di- <i>t</i> -amyl-4-hydroxyphenylmercapto)-propane	0

45

45

BEST AVAILABLE COPY

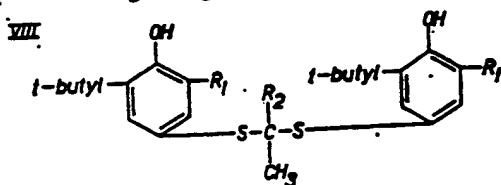
2,2-Bis-(3,5-diisopropyl-4-hydroxyphenylmercapto)-propane	0
2,2-Bis-(2-methyl-5- <i>t</i> -butyl-4-hydroxyphenylmercapto)-propane	0
2,2-Bis-(3-bromo-5- <i>t</i> -butyl-4-hydroxyphenylmercapto)-propane	0
2,2-Bis-(3- <i>t</i> -butyl-5- <i>t</i> -octyl-4-hydroxyphenylmercapto)-propane	0
2,2-Bis-(3,5-dibromo-4-hydroxyphenylmercapto)-propane	0
1,1-Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-propane	0
Bis-(3,5-di- <i>t</i> -butyl-4-hydroxyphenylmercapto)-methane	0

The compounds of the present invention are useful for reducing the level of cholesterol in the blood of warm-blooded animals. They may be employed directly in suitable dosage, or as the active ingredient in a feed composition, or with suitable nontoxic carriers. Good results are obtained with dosages of from 15 to 600 milligrams of active compound per kilogram of body weight of the recipient to provide a total intake of up to 3000 mg/kg per 24 hours.

The compounds made by the process of this invention have the utilities generally characteristic of bisphenolic and thiobisphenolic compounds. Thus, they may be used as intermediates in the preparation of a wide variety of materials such as rubber accelerators, flotation agents, dye intermediates, pharmaceuticals, lubricant additives; or they may be used in one or more of the categories of anti-oxidants, i.e. for rubber, plastics, fats, petroleum products and other organic materials normally subject to oxidative deterioration.

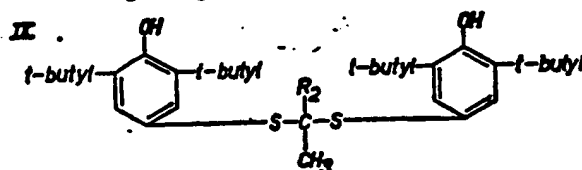
WHAT WE CLAIM IS:—

1. A compound having the general formula:



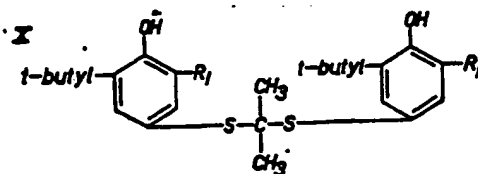
where R_1 is an alkyl group containing 1 to 4 carbon atoms, R_2 is hydrogen or an alkyl group containing 1 to 3 carbon atoms and the group *t*-butyl is a tertiary butyl group.

2. A compound having the general formula:



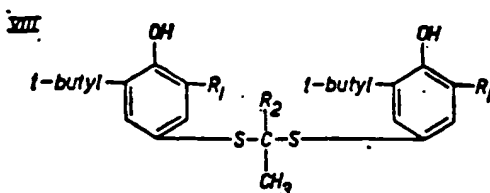
where R_2 is hydrogen or an alkyl group containing 1 to 3 carbon atoms and *t*-butyl represents a tertiary butyl group.

3. A compound having the general formula:

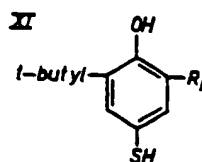


where R_1 is an alkyl group containing 1 to 4 carbon atoms and *t*-butyl is a tertiary butyl group.

4. 2,2-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-propane.
5. 2,2-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-butane.
6. 2,2-Bis-(3-*t*-butyl-5-methyl-4-hydroxyphenylmercapto)-propane.
7. 2,2-Bis-(3-isopropyl-5-*t*-butyl-4-hydroxyphenylmercapto)-propane.
8. 2,2-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-pentane.
9. 1,1-Bis-(3,5-di-*t*-butyl-4-hydroxyphenylmercapto)-ethane.
10. A method of making alkylidenedithiobisphenols having the general formula:



where R_1 is an alkyl group containing 1 to 4 carbon atoms, R_2 is hydrogen or an alkyl group containing 1 to 3 carbon atoms, and t-butyl is a tertiary butyl group, which method comprises reacting a mercaptophenol of the general formula:



wherein R_1 and t-butyl are as hereinbefore defined in this Claim, with a carbonyl compound of the formula $R_2\text{CH}_2\text{CO}$, in the presence of an acid catalyst.

11. A method as claimed in claim 10 wherein the acid catalyst is a strong acid catalyst.

12. A method as claimed in claims 10 or 11, wherein the acid catalyst is hydrochloric acid.

13. A method as claimed in claims 10 or 11, wherein the acid catalyst is perchloric acid or phosphoric acid.

14. A method as claimed in claims 10 or 11, wherein the acid catalyst is a strong acid cationic exchange resin.

15. A method of making alkylidenedithiobisphenols substantially as hereinbefore described.

16. Alkylidenedithiobisphenols whenever prepared by a method as claimed in any one of claims 10 to 15.

CONSOLIDATION COAL COMPANY,

Per: Boulton Wade & Tennant,

112 Hatton Garden, London, E.C.1.

Chartered Patent Agents.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

BEST AVAILABLE COPY

THIS PAGE BLANK (USPTO)